

Quality of Life in Patients Undergoing Salvage Procedures for Locally Recurrent Prostate Cancer

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Background and Objectives: As patients are being treated for prostate cancer at a younger age, a significant number of them will ultimately fail the primary treatment and will be candidates for potentially curative salvage therapy. The purpose of this study was to evaluate the impact of salvage therapy for locally recurrent prostate cancer upon the patients' quality of life.

Methods: A cohort of 68 men with locally recurrent prostate cancer undergoing salvage treatment was included in this analysis. Data were collected for the study by mailing the subjects a self-administered questionnaire that included a General Functional Assessment of Cancer Therapy (FACT-G) and a Prostate Cancer Treatment Outcome Questionnaire (FACT-P). Group comparisons were conducted using one-way analysis of variance (ANOVA).

Results: Overall, 50% and 88.6% of patients were free of biochemical recurrence in the salvage surgery (SS) and salvage radiotherapy (SRT) group, respectively ($P = 0.4$). The physical well-being (PWB) subscale of FACT-G was significantly higher for the SRT patients ($P = 0.008$). Using the Trial Outcome Index Prostate subscale, the Trial Outcome Index Incontinence Urinary scores, and the Functional Assessment of Incontinence Therapy-Urinary score group comparisons, patients in the SRT group had a higher quality of life than patients in the SS group ($P = 0.038$, $P = 0.001$, and $P = 0.001$, respectively).

Conclusions: In the current study, patients with clinically localized prostate cancer who are at high risk for local disease recurrence may have a trend toward better disease-free survival and a better urinary continence rates if the primary treatment is radical prostatectomy rather than radiation therapy. *J. Surg. Oncol.* 1998;69:156–161. © 1998 Wiley-Liss, Inc.

KEY WORDS: radical prostatectomy; radiotherapy; salvage procedures; quality of life

INTRODUCTION

Classically, outcome from cancer therapy has been measured by patient survival following treatment. It is becoming clear that results in the treatment of cancer should not only be reported in terms of disease-free survival, but also in terms of treatment side effects and health-related quality of life issues [1–5]. Health-related

quality of life refers to how well an individual functions in life and to his own perception of well-being [6,7].

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The widespread acceptance of prostate cancer screening leading to greater disease awareness by the general public has led to a dramatic increase in the number of men diagnosed with prostate cancer. Standard potentially curative treatments for localized prostate cancer have included radiotherapy and radical prostatectomy. Because there is no randomized clinical trial that supports the superiority of either radical prostatectomy or radiotherapy in the treatment of clinically localized prostate cancer, patients have placed emphasis in the potential impact of the treatment on their quality of life (QOL). Many studies have investigated and compared life adjustment after radical prostatectomy, radiotherapy, and hormonal therapy as the primary treatment [1–5,7]. The widespread use of serum prostate-specific antigen (PSA) in the follow-up of patients treated for prostate cancer can identify disease recurrence years before clinical manifestations or metastatic disease occurs [5,8,9]. A local recurrence detected following primary definitive treatment for prostate cancer can be treated with salvage procedures [8,9]. As patients are being treated at a younger age for clinically localized prostate cancer, a significant number of them will ultimately fail primary treatment and will be candidates for potentially curative salvage therapy. Limited information exists on patient-reported QOL and severity of treatment-related side effects following salvage treatment for locally recurrent prostate cancer. The purpose of this study was to determine the impact of salvage procedures upon QOL and evaluate the iatrogenic effects of treatment in patients with locally recurrent prostate cancer.

MATERIAL AND METHODS

Subjects

A retrospective chart review was done on 108 patients with locally recurrent prostate cancer undergoing salvage treatment at the Wayne State University and Barbara Ann Karmanos Cancer Institute affiliated Harper Hospital between December 1989 and December 1995. Patients' selection criteria included: histologically diagnosed adenocarcinoma of the prostate; clinically localized prostate cancer treated primarily with curative intention with radiotherapy or radical prostatectomy; an isolated biochemical recurrence without clinical evidence of metastatic disease; and patients had to be currently alive. A final cohort of 68 men who met all eligibility criteria was included in the analysis. All patients were able to read and write English.

A radical retropubic prostatectomy was performed on 44 patients and radiation therapy was done on 24 patients as primary treatment. Salvage therapy consisted of surgery in the radiation therapy treated group and external beam radiation therapy in the surgically treated group. All patients treated with salvage surgery (SS) had biopsy-confirmed recurrent adenocarcinoma of the pros-

tate. Salvage radical prostatectomy was done in 21 patients and salvage cystoprostatectomy with urinary diversion was performed in three patients. Salvage radiotherapy (SRT) was delivered with a median cumulative dose of 65 Gy utilizing high-energy photons to the prostatic fossa. All of these patients had an elevated PSA (>0.4 ng/mL) after radical prostatectomy. Biopsy of the prostatic bed was not routinely performed. Biochemical disease recurrence after salvage therapy was defined as serum prostate-specific antigen (PSA) level >0.4 ng/mL.

Measures and Method of Analysis

Data were collected for the study by mailing the subjects a self-administered questionnaire. A letter of introduction and a prestamped return envelope were sent together. Telephone reminders were used for all patients who did not respond within 4 weeks of sending the survey, and another questionnaire was sent to those who did not respond. The questionnaires were coded to ensure patient confidentiality. If patients did not return the second mailed questionnaire, no further contact was attempted.

The self-administered questionnaire used in this study included a General Functional Assessment of Cancer Therapy (FACT-G) and a Prostate Cancer Treatment Outcome Questionnaire (FACT-P). These self-reported questionnaires were previously validated and tested for reliability [7,10,11]. Patients provided information in five areas of well-being: physical (PWB), social/family (SWB), emotional (EWB), functional (FWB), and relationship with doctor (RWD). The questionnaire was answered by patients choosing just one among five options, ranked from "not at all" to "very much." They selected a response that best represented their opinion of how true each statement was for them within the past 7 days.

The five areas of well-being that make up the subscale combinations of the 28 items in the FACT-G instrument were computed using the published scoring procedure [10]. The five experimental items in the FACT-G (version 3) instrument were not scored. Scores for the cancer-specific subscale (12 items) for patients with prostate cancer (FACT-P) and the symptom-specific subscale (11 items) for functional assessment of incontinence therapy-urinary (FAIT-U) were computed in a similar manner. Two separate a priori indices were identified. The trial outcome index using prostate cancer subscale (TOI-P) was defined as the sum of physical well-being (PWB), functional well-being (FWB), and FACT-P scores. The trial outcome index using incontinence-urinary subscale (TOI-U) was defined as the sum of physical well-being (PWB), functional well-being (FWB), and FAIT-U scores [10,11].

The group mean and variance were computed for each subscale for both the SS patients and the SRT patients (SPSS base 7.5 for windows (Version 7.5), 1997, Chi-

TABLE I. Clinical Data Comparison Between Patients Undergoing Salvage Procedures

| | Salvage surgery | Salvage radiotherapy | P value |
|--|-----------------|----------------------|---------|
| Age (years) | 66.2 | 65.7 | 0.9 |
| Median follow-up (months) | 36.1 | 37.2 | 0.22 |
| Pretreatment clinical stage ^a | | | |
| T1c | 5 | 3 | |
| T2a | 4 | 17 | |
| T2b | 6 | 17 | |
| T2c | 9 | 7 | |
| Mean Gleason score before salvage ^b | 7.1 (5–8) | 6.73 (5–10) | 0.08 |
| Mean PSA level before salvage | 8.9 (1.2–18.41) | 1.12 (0.5–12.5) | 0.001 |
| Disease-free survival ^c | 12/24 (50%) | 39/44 (88.6%) | 0.4 |
| Response rate | 24/24 (100%) | 39/44 (88.6%) | 0.2 |

^aSalvage surgery group—clinical stage before initial radiotherapy; salvage radiotherapy group—clinical stage before standard radical prostatectomy.

^bSalvage surgery and salvage radiotherapy group/radical prostatectomy specimen.

^cDefined based on biochemical criteria (PSA level <0.4 ng/mL) and calculated by Kaplan-Meier method.

cago). Group comparisons using the five FACT-G areas of well-being, FACT-P scores, FAIT-U scores, and corresponding indices were conducted using one-way analysis of variance (ANOVA). Alpha level of significance of 0.05 was used for the analysis.

RESULTS

Clinical data regarding patients included in this study are summarized in Table I. There was no difference between these two groups in age, length of follow-up, pretreatment clinical stage, and mean Gleason score in the radical prostatectomy specimen. A statistically significant difference was noted in the mean serum PSA level before salvage treatment in the SS group (8.9 ng/mL) compared to the SRt group (1.12 ng/mL) ($P = 0.001$). Overall, 12 of 24 (50%) and 39 of 44 (88.6%) patients were free of biochemical recurrence in the SS and SRt group, respectively, with a mean follow-up of 37 months after salvage treatment. Of the 68 questionnaires mailed, 63 patients replied (92.6%). The number of responding patients was 24 (100%) for the SS group and 39 (88.6%) for the SRt group.

The FACT-G summary scores from the returned questionnaires ranged from 50 to 110 (highest possible score 112). Table II shows the mean scores and variances for each FACT-G and FACT-P subscale comparison between SS and SRt. The PWB subscale of FACT-G showed that the SRt patients had a significantly higher PWB than the SS patients ($F(1,61) = 7.60$, $P = 0.008$). There was no difference between the groups regarding emotional or SWB issues, including feelings of anxiety, sadness, losing the fight against the illness, or worries about dying ($P = 0.6$). Group comparisons of the four remaining FACT-G subscales did not show any statistically significant difference in scores between the two treatment groups. The overall FACT-G, FACT-P, FACT-Total scores showed no statistically significant difference

TABLE II. Comparison of Quality of Life Measures (FACT-G, FACT-P, and FAIT-U) Between Salvage Surgery and Salvage Radiotherapy

| | Mean score (standard deviation) | | P value |
|-------------------------|---------------------------------|----------------------------------|---------|
| | Salvage surgery (n = 24) | Salvage radiotherapy (n = 39) | |
| PWB ^a | 21.88 (5.01) | 25.28 (2.89) | 0.008 |
| SWB ^b | 22.61 (3.62) | 20.47 (6.37) | 0.138 |
| RWD ^c | 7.04 (1.33) | 6.87 (1.73) | 0.664 |
| EWB ^d | 16.42 (2.89) | 16.82 (3.14) | 0.604 |
| FWB ^e | 20.71 (4.96) | 21.79 (5.91) | 0.436 |
| FACT-G ^f | 88.65 (14.17) | 91.24 (12.11) | 0.462 |
| FACT-P ^g | 33.25 (6.44) | 35.74 (6.14) | 0.136 |
| FACT-Total ^h | 121.95 (19.2) | 126.98 (16.38) | 0.288 |
| TOI-P ⁱ | 75.83 (14.74) | 82.82 (11.33) | 0.038 |
| FAIT-U ^j | 24.04 (9.56) | 31.05 (5.7) | 0.001 |
| FACT-Total ^k | 112.69 (20.53) | 122.29 (15.04) | 0.054 |
| TOI-U ^l | 66.63 (16.58) | 78.13 (10.89) | 0.001 |

^aPhysical well-being.

^bSocial/family well-being.

^cRelationship with doctor.

^dEmotional well-being.

^eFunctional well-being.

^fPWB + SWB + RWD + EWB + FWB.

^gProstate cancer subscale.

^hFACT-G + FACT-P.

ⁱTrial Outcome Index (PWB + FWB + FACT-P).

^jIncontinence-Urinary Subscale.

^kFACT-G + FAIT-U.

^lTrial Outcome Index (PWB + FWB + FAIT-U).

between treatment groups. The TOI-P group comparisons showed a statistically significant difference indicating a higher quality of life for SRt patients ($F(1,61) = 4.48$, $P = 0.038$).

We analyzed the urinary continence status following salvage procedures with the FAIT-U and TOI-U scores. SRt patients scored significantly better than SS patients in the FAIT-U and TOI-U scores ($F(1,61) = 13.34$, $P = 0.01$ and $F(1,61) = 11.08$, $P = 0.01$, respectively)

TABLE III. Aspects of Urinary Continence in Patients Undergoing Salvage Procedures

| | Salvage surgery (24) | Salvage radiotherapy (39) | <i>P</i> value |
|---|----------------------------|---------------------------|----------------|
| Complete urinary continence ^a | 9/21 (42.9%) ^b | 26/39 (66.7%) | 0.01 |
| Mild urinary incontinence (<3 pads/day) ^a | 9/21 (42.9%) ^b | 12/39 (30.8%) | 0.1 |
| Severe urinary incontinence (>3 pads/day) | 3/21 (14.3%) ^b | 1/39 (2.6%) | 0.01 |
| I am afraid to be far from the toilet | 11/24 (45.8%) | 20/39 (51.3%) | 0.67 |
| I must urinate frequently to avoid leakage | 6/9 (66.7%) | 17/26 (65.4%) | 0.9 |
| My problems with urinating limit my activities | 13/24 (54.2%) | 17/39 (43.6%) | 0.75 |
| I wear any kind of protection for leakage of urine ^c | 12/21 (57.1%) ^b | 13/39 (33.3%) | 0.01 |

^aObtained retrospectively from chart review.^bThree patients excluded from analysis (ileal loop urinary diversion).^cInformation obtained from questionnaire.

(Table II). SS patients had greater voiding frequency, more leakage, more pads used per day to control leakage, and more limitations in daily activities due to urinary leakage than SRt patients (Table III). Three of 24 (12.5%) patients in the SS group had cystoprostatectomy with ileal loop urinary diversion, and they were excluded from the final analysis in terms of urinary continence. Nine of 21 (42.9%) patients achieved complete urinary continence after SS compared to 26 of 39 (66.7%) patients after SRt ($P = 0.01$). Nine of 21 (42.9%) patients undergoing SS used 1–3 pads/day. Three of 21 (14.3%) used more than 3 pads/day, of whom one subsequently had an artificial urinary sphincter implanted. In the SRt group, 12 of 39 (30.8%) and 1 of 39 (2.6%) used 1–3 and >3 pads/day, respectively. Among patients who achieved continence after salvage treatment, 6 of 9 (66.7%) patients in the SS group urinated frequently to avoid leakage, compared to 17 of 26 (65.4%) in the SRt group ($P = 0.9$). There was no difference in the number of patients who answered that they were afraid to be far from a toilet between the two groups; 11 of 24 (45.8%) SS patients and 20 of 39 (51.3%) SRt patients ($P = 0.67$). Also, there was no difference between the two groups in the number of patients who felt that problems with urinating limited their activities; 13 of 24 (54.2%) SS and 17 of 39 (43.6%) SRt patients ($P = 0.75$).

We looked at our descriptive results regarding answers to the questions: “Have you been sexually active during the past year?” and “Are you able to have and keep an erection?” Based on the answers to these questions, the

vast majority of patients are impotent in both groups. One of 24 (4.1%) patients in the SS group was potent following salvage radical prostatectomy without any kind of treatment (i.e., intracavernosal injection, prosthesis, vacuum device). Similarly, 4 of 39 (10.2%) SRt patients reported spontaneous erections enough for sexual intercourse without any kind of treatment. There was no statistically significant difference regarding sexual potency between groups ($P = 0.6$). Formal tumescence studies were not conducted to corroborate these findings and the information about treatment for sexual potency was obtained by chart review or telephone interview.

Finally, patients were asked, “Are you content with the quality of your life right now?” Of 24 patients in the salvage surgery group, 18 (75%) answered: 9 were somewhat content, 6 were quite a bit content, and 3 were very much satisfied with quality of life. In the salvage radiotherapy group of 39 patients, 25 (64.1%) answered: 11 were somewhat content, 9 were quite a bit content, and 5 were very much satisfied with their quality of life.

DISCUSSION

The advent of multimodality treatments for cancer combining surgery, radiation therapy, and chemotherapy have markedly improved the prognosis of many forms of cancer. When evaluating QOL in cancer patients, tension arises between the need to obtain general information about health status, which is relatively independent of the nature of the illness or treatment being delivered, and the need to obtain information about health status that is specific to a given illness or treatment. Information gathered from a self-administered questionnaire may reflect a more accurate picture of patient condition and decrease observer-based bias.

As comparable treatment options for prostate cancer are developed, it becomes important to analyze the treatment impact on the patient's QOL. This allows patients to make more informed treatment decisions [12,13]. Patients with an isolated local recurrence after surgery or radiotherapy can be treated with salvage therapy in an attempt to cure their disease [8,9]. However, acute and chronic toxicity has been associated with these approaches. Measurement of patient function has become a necessary component of outcome evaluation in many clinical trials. This study focused on survivors of locally recurrent prostate cancer treated with salvage procedures 1–5 years after initial treatment. Therefore, we can identify long-term QOL differences between the two groups. The acute toxicity associated with each treatment has previously been reported [9,14]. The FACT-G, chosen to measure general well-being, did not show overall significant differences in quality of life between the two treatment groups. However, there were significant differences, as measured by the FACT-P, between salvage surgery and salvage radiotherapy. The SS group fared

worse in the areas of PWB ($P = 0.008$), TOI-P ($P = 0.038$), FAIT-U ($P = 0.001$), and TOI-U ($P = 0.001$) compared to patients undergoing SRt. The PWB and TOI-P results suggest that SRt patients have a better QOL than SS patients. This is probably primarily related to urinary incontinence. The FAIT-U is a symptom-specific subscale that give us the functional assessment of urinary incontinence following treatment. SS patients were found to have significantly more treatment-related urinary symptoms and leakage than the SRt patients. SS patients reported more leaking, increased leaking with coughing or sneezing, and greater use of protection than the SRt patients. Regarding sexual potency, both groups had a high incidence of impotence following salvage procedure (96% and 90%, following SS and SRt, respectively). These data reflect the long-term complications related to treatment of locally recurrent prostate cancer in both SS and SRt groups.

Salvage prostatectomy patients had significantly worse PWB than did patients who received SRt ($P = 0.008$). Salvage prostatectomy patients complained more of lack of energy, and they were more bothered by treatment side effects. Conversely, when we looked at functional well-being item questions, we found no difference between these two study groups ($P = 0.4$). This means that both groups of patients were able to work and enjoy activities that they usually did for pleasure. However, the salvage radical prostatectomy group had more limitation in daily activities due to urinary leakage.

Despite the differences in continence and PWB, 75% of patients in the SS group answered that they are somewhat/quite a bit/very much satisfied with their QOL, compared to 64% of patients in the SRt group. This degree of satisfaction expressed by this series of patients may be a reflection of the time that treating physicians spent explaining the benefits and potential complications of therapy. These findings may also reflect a certain degree of acceptance of the illness by patients or, perhaps, their determination to live despite a local recurrence following initial treatment failure. The high response rate (92.6%) among our patients strongly suggests that they value these issues and are willing to communicate their feelings about the most intimate aspects of their lives. Therefore, this validates the concept that QOL is an important disease-targeted measure and should be included in future clinical trials of prostate cancer treatments.

With early prostate cancer detection programs, men are being diagnosed at a younger age and with an 80–90% chance of having clinically localized disease [15]. Most of these patients will be treated with either surgery or radiotherapy. Despite this aggressive treatment, ~30% of patients will have a disease relapse [16,17]. Currently available pretherapy prognostic factors indicate that men with serum PSA >10 ng/ml and a Gleason score equal to or higher than 7 have a high risk of extraprostatic disease

and possibly subsequent disease relapse [16–18]. Patients with these preoperative parameters constituted ~45% of radical prostatectomies performed at our institution from 1991–1996. From a QOL point of view, it appears that primary radical prostatectomy followed by SRt is better tolerated and has less impact upon quality of life than the converse. This is important because there was no difference in the disease-free survival rate between the two groups. Therefore, QOL issues may be the main determinant of treatment.

Because of the retrospective nature of this study, information regarding pretreatment physical function (sexual potency, urinary continence, and bowel function) is not available. This limitation prevents us from obtaining pretreatment and posttreatment scores on variables that reflect functional status. We attempted to gather this information with some additional questions by asking if patients had any problem with bowel, urinary, or sexual function before or following initial prostate cancer treatment. However, this open-ended question made responses difficult to analyze. A future prospective study could eliminate this problem with baseline health measure. Physicians need to be aware of patient-reported outcome studies in order to counsel patients on the benefits and risks associated with initial treatment failure and options of salvage. A well-informed patient can be more involved in the treatment decision and more accepting of the frequency and severity of the salvage treatment side effects and the impact on his future quality of life.

CONCLUSION

It is clear that salvage procedures may be accompanied by some morbidity and thus may be associated with a decreased quality of life. In the current study, patients with clinically localized prostate cancer who are at high risk for local disease recurrence may have a trend toward better disease-free survival and a better urinary continence rates if the primary treatment is radical prostatectomy rather than radiation therapy. This information should be incorporated in the decision-making process for patients at high risk of disease recurrence following primary therapy.

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